REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claims 6, 7, 11, 14, 15, and 30 have been amended. Support for these amendments can be found throughout the specification, including at page 9, lines 22-29 and at page 10, lines 1-11. No new matter has been added through the amendments.

Upon entry of the Amendment, claims 6-18, 21-25, and 29-31 will be pending. Applicants respectfully request reconsideration and withdrawal of the pending rejections under 35 U.S.C. §§ 102(b), 103(a), and 112, second paragraph.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 11 and 30 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner alleges that the limitation "a pharmaceutically acceptable liver-targeting substance" renders the claim indefinite. Although Applicants do not agree, Applicants have amended claims 11 and 30 to replace "a pharmaceutically acceptable liver-targeting substance" with "albumin, liposomes and bile salts". Support for this amendment can be found at page 10, lines 1-11. In view of the amendments, this rejection is now moot and should be removed.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejects claims 6-8, 29, and 30 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,436,996 B1 (Vitek *et al.*). The Examiner asserts that Vitek discloses a composition comprising SIN-1 and N-acetylcysteine (claim 1, column 9, lines 5-8) as an exogenous source of increasing the nitric oxide levels in cells in Alzheimer's patients who suffer from decreased nitric oxide levels associated with the presence of an APOE4 allele. Applicants respectfully traverse the rejection under 35 U.S.C. § 102(b).

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention, arranged as in the claim." *Lindemann Mashinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *See also*, MPEP §2131. Applicants respectfully assert that the '996 patent does not disclose each and every

element of amended claim 1. Vitek et al. do not disclose therapeutically effective amounts of glutathione increasing or hepatic nitric oxide increasing compounds for reducing insulin resistance. The '996 patent only describes the treatment of diseases associated with the presence of an APOE4 allele. Additionally, Vitek et al. do not disclose a combination of compounds. As cited by the Examiner, claim 1 of the '996 patent recites both SIN-1 and N-acetylcysteine. However, both compounds are recited within a Markush group, and the Markush group does not recite "combinations" or "mixtures" thereof. Thus, the claim is limited to selection of one of the compounds and excludes combinations thereof. Additionally, there is no support or recitation for a combination of compound in the specification of the '996 patent. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Additional Arguments

The Examiner rejected claims 6-8, 29, and 30 under 35 USC 102(b) as being anticipated by US Patent No. 6,436,996 to Vitek et al. The Examiner stated that the Applicants presently claim a pharmaceutical composition comprising N-acetylcysteine and SIN-1 as glutathione increasing and nitric oxide increasing compounds respectively. The Examiner stated that Vitek discloses a composition comprising SIN-1 and N-acetylcysteine (claim 1, column 9, lines 5-8) as an exogenous source of increasing the nitric oxide levels in cells in Alzheimer's patients who suffer from decreased nitric oxide levels associated with the present of APOE4 alleles. The Examiner took the position that the disclosed composition comprises species elected in the present invention and would, when administered, perform the desired glutathione increasing and nitric oxide increasing functions.

It is respectfully submitted that the subject matter of claims 6-8, 29, and 30 are not anticipated. Vitek teaches a method for treating Alzheimer's disease which comprises the determination of whether the patient carries at least one APOE4 allele, and administrating to a patient which has been determined to have an APOE4 allele, an exogenous source of nitric oxide such as SIN-1 or N-acetylcysteine. The Examiner stated that claim 1 discloses a composition comprising N-acetylcysteine and SIN-1 (emphasis added). Applicant notes that claim 1 only teaches the use of N-acetylcysteine or SIN-1 in the alternative and does not include language suggesting the use of combinations thereof. The specification also fails to suggest the use of any

of the disclosed exogenous sources of nitric oxide in combination. Accordingly, it is respectfully submitted that Vitek does not disclose a composition comprising SIN-1 and N-acetylcysteine as asserted by the Examiner. Accordingly, the Applicant maintains that the subject matter of the claims is not anticipated by Vitek. As set out in the present application (see example page 6, first paragraph), the present invention is based on the discovery that it is the combined action of glutathione increasing compounds and no increasing compounds that increase HISS production in the liver. This is not suggested or anticipated by the prior art.

With respect to claim 7, the Applicant notes that the defined pharmaceutical composition optionally comprises nitrosylated N-acetylcysteine (emphasis added). Vitek only teaches the use of N-acetylcysteine and thus does not anticipate claim 7 nor its dependent claims 29 or 30. With respect to claim 30, it is noted that the claim has been amended to recite the further inclusion of albumin, liposomes, or bile salts. None of these compounds are discloses or suggested in Vitek.

Claims 8, 29, and 30 are all dependent on claim 7.

In view of the preceding reasons, it is respectfully submitted that claims, 6, 7, 8, 29, and 30 are not anticipated by Vitek. Reconsideration and withdrawal of the Examiner's rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejects claims 6-17, 21, 23-25, and 29-31 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. 6,436,996 B1 (Vitek *et al.*) in view of Mattia *et al.*, *Dibetologia*, 1998, 41:1392-1396 and further in view of WO 00/19992 (Lautt *et al.*). Applicants respectfully traverse the rejection under 35 U.S.C. § 103(a).

To establish a *prima facie* case of obviousness, three criteria must be met--a suggestion or motivation to combine references, a reasonable expectation of success, and the prior art reference teaches or suggests all the claim limitations. MPEP §2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Applicants respectfully assert that the Examiner has not established a suggestion or motivation to combine the references, and the prior art does not teach or suggest all of the claim limitations. The cited art does not teach or suggest a therapeutically effective amount for reducing insulin resistance of a hepatic glutathione increasing compound. Additionally, Applicants respectfully assert that there is no motivation to combine a reference

(Lautt et al.) that discloses a therapeutically effective amount for reducing insulin resistance of a nitric oxide increasing compound with a therapeutically effective amount for treating diseases associated with the APOE4 allele (Alzheimer's, ALS, etc.) of a glutathione increasing compound. Applicants respectfully assert that combining a reference describing the treatment of Alzheimer's disease with WO 00/19992 to arrive at the instant claims could only result from hindsight reconstruction. *In re Oetiker*, 977 F.2d 1443, 1446 (Fed. Cir. 1992). Applicants respectfully assert that the Examiner has not met the criteria for establishing obviousness under 35 U.S.C. §103(a) and respectfully request removal of this rejection.

Additional Arguments

In reply to the Applicant's obligation under 37 CFR 1.56, the Applicant advised that all the claims are commonly owned and share the same inventors and invention date.

The Examiner rejected claims 6-17, 21, 23-25, and 29-31 under 35 USC 103(a) as being unpatentable over US 6,436,996 to Vitek et al., in view of Mattia et al. and in further view of WO 00/19992 to Lautt et al. The Examiner stated that the Applicant claims a pharmaceutical composition comprising N-acetylcysteine and SIN-1 and a method of administering the pharmaceutical composition for reducing insulin resistance in mammalian patients having lower than normal glutathione concentration, wherein N-acetylcysteine acts as a glutathione increasing compound and SIN-1 acts as a nitric oxide increasing compound. The Examiner stated that Vitek et al. discloses a composition containing N-acetylcysteine and SIN-1 but does not teach that the composition is for use in the method of reducing insulin resistance in patients having lower than normal hepatic glutathione levels.

The Examiner stated that Mattia et al. shows that the administration of N-acetylcysteine increases the glutathione and GSII/GSSG ratio concentration in non-insulin dependent diabetic patients and that Lautt et al. teaches the administration of nitric oxide increasing compounds such as SIN-1 to stimulate nitric oxide in the liver and provides a method for increasing insulin sensitivity.

The Examiner stated that it would have been obvious to the person skilled in the art to combine the methods taught by Vitek, Mattia and Lautt to design a method for the treatment of non-insulin dependent diabetes. The Examiner stated that the motivation comes from the fact

that the mechanism for non-insulin dependent diabetes involves both increases in glutathione concentration and a nitric oxide enhancement. The Examiner stated that Mattia teaches the use of N-acetylcysteine for increasing glutathione concentration and Lautt teaches the use of SIN-1 for increasing the nitric oxide concentration and treating non-insulin dependent diabetes. The Examiner (erroneously) stated that even though Vitek teaches the use of the *combination* of N-acetylcysteine and SIN-1 for conditions such as Alzheimers, that this reference provides a reasonable expectation of success as the combination increase nitric oxide levels in cells in diseases such as Alzheimers disease.

In reply to the Applicant's obligation under 37 CFR 1.56, the Applicant advises that all the claims are commonly owned and share the same inventors and invention date.

It is respectfully submitted that none of the cited prior references taken together or alone, make obvious the claimed subject matter of claims 6-17, 21, 23-25, and 29-31.

Vitek teaches a method for treating Alzheimer's disease which comprises the determination of whether the patient caries at least one APOE4 allele, and administrating to a patient which has been determined to have an APOE4 allele, an exogenous source of nitric oxide such as SIN-1 or N-acetylcysteine. Vitek further teaches that the disclosed method of treatment may be carried out in patients afflicted with HIV dementia, multiple sclerosis, amyotropic lateral scelerosis, rheumatoid arthritis, or inflammatory bowel disease. Vitek teaches that the administration of an exogenous source of nitric oxide to combat the decrease of in cellular nitric oxide levels associated the present of at least one APOE4 allele. Vitek teaches that that the treatment of cells (i.e. macrophages or glia cells) carrying at least one APOE4 allele with an exogenous source nitric oxide combats or inhibits the effects of stress, and in particular oxidative stress, and thereby prolongs cell life and/or enhances normal function of the cells being treated. Thus, Vitek merely teaches a method of treatment for diseases associated with present of at least one APOE4 cells for with an exogenous source of nitric oxide for combating or inhibiting cell stress. As the Examiner has acknowledged, there is no teaching or suggestion that the administration of one or more of disclosed exogenous sources of nitric oxide would be useful for the treatment of insulin resistance, diabetes or any other metabolic disorder.

Mattia discloses the effect of N-acetylcysteine treatment in otherwise healthy, non-insulin dependent diabetics. Mattia discloses that in non-insulin dependent diabetics, both oxidative

stress and plasma soluble VCAM-1 (which is known in the art as an inflammation marker) concentrations are raised suggesting that they might be interrelated. The authors set out to determine whether treatment with the antioxidant agent N-acetylcysteine was effective for reducing circulating soluble VCAM-1 in non-insulin dependent diabetics. Mattia discloses the assessment of GSH and GSSG concentration and GSH:GSSG ratio as indexes of oxidative stress. In the discussion, Mattia discloses that in otherwise healthy non-insulin dependent diabetics, circulating VCAM-1 concentrations were elevated and that there was a negative correlation between plasma soluble VCAM-1 and GSH concentrations suggesting that augmented oxidative stress was responsible for VCAM-1 upregulation. Mattia further discloses that N-acetylcysteine treatment reduced VCAM-1 and intraerythrocytic GSSG concentrations and increased intraerythrocytic GSH levels and the GSH:GSSG ratio. In view of the experimental findings, the authors suggest that increased oxidative stress causes early endothelial activation in non-insulin dependent diabetic patients and that N-acetylcysteine down regulates VCAM-1 by reducing oxidative stress. The authors further speculate that since VCAM-1 is known to represent a fundamental step in atherogenesis, antioxidant treatment, i.e. N-acetylcysteine, may be useful for protecting against the onset of diabetes-related vascular damage by inhibiting VCAM-1 related monocyte and lymphocyte intravascular accumulation.

While Mattia speculates that antioxidant agents may be useful in protecting against endogenous oxidant-related upregulation of endothelial adhesion molecules and slowing down the progression of vascular damage in non-insulin dependent diabetes, there is no teaching or suggestion that N-acetylcysteine or any other glutathione increasing compound would be useful for reducing insulin resistance in a mammalian patient have lower than normal hepatic glutathione levels. GSH levels are disclosed in Mattia merely as an index for oxidative stress. There is no teaching or suggestion that GSH levels or oxidative stress are related to insulin sensitivity or resistance. The person skilled in the art having regard to Mattia would only conclude that N-acetylcysteine treatment is effective for reducing oxidative stress in non-insulin dependent patients and may be useful for treating diabetes related vascular damage.

Lautt discloses a method for increasing insulin sensitivity comprising the administration of an effective amount of a compound which stimulates nitric oxide production in the liver. There is no teaching or suggestion that insulin resistance is related to lower than normal hepatic

glutathione levels. There is no teaching or suggestion of the use of any glutathione increasing compound for either increasing insulin sensitivity or for reducing insulin resistance.

The Examiner took the position it would have been obvious to the person skilled in the art to combine the methods taught by Vitek, Mattia and Lautt to design a method for the treatment of non-insulin dependent diabetes. The Examiner stated that the motivation comes from the fact that the mechanism for non-insulin dependent diabetes involves both increases in glutathione concentration and a nitric oxide enhancement. The Examiner stated that Mattia teaches the use of N-acetylcysteine for increasing glutathione concentration and Lautt teaches the use of SIN-1 for increasing the nitric oxide concentration and treating non-insulin dependent diabetes. The Examiner stated that even though Vitek teaches the use of the combination of N-acetylcysteine and SIN-1 for conditions such as Alzheimers, that this reference provides a reasonable expectation of success as the combination increase nitric oxide levels in cells in diseases such as Alzheimers disease.

As evident from the above discussion of the cited prior art, the references do not provide the motivation asserted by the Examiner. While Mattia does disclose that N-acetycysteine treatment increases intraerythrocytic levels of GSH in otherwise healthy non-insulin dependent diabetics, there is no teaching or suggestion that increased GSH levels are correlated with reduced insulin resistance or any other metabolic disorder, let alone any suggestion that increasing hepatic glutathione levels would be useful for treating insulin resistance. Thus, contrary to the Examiner's assertion, Mattia fails to teach or suggest the usefulness of glutathione increasing compounds for the treatment of insulin resistance. Mattia merely teaches the use of N-acetylcysteine as an antioxidant for reducing VCAM-1 levels and the treatment of diabetes related vascular disorders. There is no suggestion in Lautt that glutathione levels, and in particular, hepatic glutathione levels, impact insulin resistance. Thus, the person skilled in the art having regard to Mattia and Lautt would have no motivation to combine the teachings for the purpose of designing a method of treating insulin resistance. Vitek does not teach or suggest the usefulness of nitric oxide donors for the treatment of any condition other than those related to the presence of at least one APOE4 allele. Accordingly, the person skilled in the art having regard to Vitek would have not motivation to adapt any of the disclosed methods of treatment for conditions other than those correlated to the APOE4 allele.

In view of the preceding reasons, reconsideration and withdrawal of the Examiner's objection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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